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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/360,242 | 07/22/1999 | JOHN R. MCDONALD | 25020-601B | 3887 |

20985 7590 04/07/2005

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| EXAMINER |
|---|
| LANDSMAN, ROBERT S |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/360,242 | MCDONALD ET AL. | |
| | Examiner | Art Unit | |
| | Robert Landsman | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *26-29,31,32,35-37,40,42,44-46,48-54,57 and 65-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 and 65-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/28/04; 8/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/18/04 has been entered.

*1. Formal Matters*

A. The Amendment dated 8/18/04 has been entered into the record.

B. The Information Disclosure Statement dated 5/28/04 has been entered into the record.

C. The Information Disclosure Statement dated 8/18/04 has been entered into the record.

D. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

E. Claims 26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 and 65-97 are pending and are the subject of this Office Action.

*2. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement*

A. Claims 26-29, 31, 32, 35-37, 40, 42, 44-46, 48-54, 57 and 65-95 remain rejected and new claims 96 and 97 are also rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 2-7 of the Office Action mailed 2/18/04.

Applicants argue that the claimed conjugates are designed to target and bind to the receptors on immune cells and to be internalized. Applicants argue that they are not claiming methods of treating all pathologies. Applicants argue that there is no reason that the conjugates should not bind to and be taken up by the cells which express the targeted receptors. Applicants argue that methods of targeting conjugates to receptors are well-known and that targeting leukocytes, in particular, is known. Applicants argue that modulation of the levels of leukocytes will interfere with and modulate a variety of pathologies.

These arguments have been considered, but are not deemed persuasive. First, as discussed in Applicants' arguments, the present invention uses methods known in the art to target conjugates to

activated leukocytes. Though it appears from Applicants' arguments that the claimed invention is well-known in the art, Applicants appear to be arguing that the present invention is distinct from the prior art in that the conjugates target activated leukocytes, not leukocytes in general. The Examiner also understands that Applicants are not claiming methods of treating any and all pathologies, but are only claiming methods of targeting activated leukocytes.

While targeting activated leukocytes is not the same as claiming a method of treating diseases, the scope remains excessive. As previously argued by the Examiner, Applicants are claiming methods of using conjugates to target activated leukocytes under any condition. *Respectfully, if Applicants' claims were to be summarized, the breadth includes methods of using all potential toxins linked to all potential chemokines to target any potential immune effector cell in any potential activation state in order to inhibit activation, proliferation or migration of these immune effector cell by altering metabolism or gene expression in the cell, regulating or altering protein synthesis in the cell, or killing the cell.*

Applicants' argument on page 18 of the Response dated 8/18/04 that "modulation of the levels of leukocytes will interfere with [and] modulate a variety of pathologies" is not persuasive. Applicants have provided only minimal evidence that this targeting procedure will work. Applicants have only provided an example of three conjugates and shown that they are effective in vitro and that, at most, one is not toxic when administered in vivo. The Examiner continues to wrestle with the assumed conclusion that, if the use of toxins-chemokine conjugates were well-known at the time of the present invention and that targeting leukocytes with conjugates was also well-known, the present invention is, in fact, predictable. If the targeting of conjugates to leukocytes was, in fact, predictable at the time of the present invention, it is not understood, since Applicants are claiming their methods are, in fact, distinct from these methods in the art, how Applicants' methods would then be predictable. It would appear that Applicants' methods are, by logical conclusion, unpredictable.

Furthermore, the scope and sheer magnitude of what Applicants are trying to tackle is further evident in the last paragraph on page 18 of the Response (see also paragraph 2 on page 25). Applicants state:

> Inappropriate triggering, disregulation or over-activation of the immune response is responsible for the damage to normal host tissue witnessed in leukocyte-mediated diseases such as arthritis, multiple sclerosis, and pulmonary diseases. Leukocyte-mediated diseases also include trauma (e.g. spinal cord injury) and cancers and others. In the latter, leukocytes exert tumorigenic effects by nourishing the cancer directly or

indirectly (by directing angiogenesis), by supplying chemokines and growth factors, and aiding metastasis by supplying various extracellular proteases.

Though Applicants continue to argue that they are not attempting to treat diseases (though this type of language was previously claimed in claim 29, for example), it remains that there is an incredibly vast role for leukocytes (and other immune effector cells which are not generally even discussed in the Response, adding to the sheer scope of the invention) in everything from cancer, to arthritis, to MS to trauma. This is far from an exhaustive list. Applicants argue on page 19 that "the inflammatory response plays [a] role in a variety of diseases." Though, again, Applicants have argued that they are not attempting to treat inflammation, or any disease, it is this argument regarding the role of inflammation that supports the vast scope of Applicants' invention.

Applicants argue the Shuh et al. teach that a RANTES-PE38 conjugate retains the functionality of RANTES, binds to its receptors and internalizes the linked toxin. This argument has been considered, but is not deemed persuasive. Shuh et al. shows that their conjugate is only effective in Chinese Hamster Ovary cells. Shuh do not teach any examples of their one conjugate having any effect in vivo. Applicant's intended use, as made evident by the specification, is for the in vivo modulation of immune effector cells.

In fact, Shuh teach on the left column of page 2421 that the full-length PE is toxic to most cells. Therefore, a truncated PE had to be produced. This is a problem that Applicant has, respectfully, not addressed. As claimed, the methods require (and recite) a targeted agent or "a portion thereof." Given the teaching of Shuh, it is clear that substantial knowledge of the individual toxins must be known in order to prevent or significantly reduce any unwanted side-effects from administration of these toxins. Furthermore, due to the scope of "targeted agent," which reads on more than toxins, it can be easily seen how a lack of guidance and working examples of these "agents" can be extrapolated to these "non-toxin" agents. Applicants have provided only minimal guidance and working examples of how to produce a toxin which has minimal side-effects and no guidance or examples of agents other than toxins. However, the claims are not limited to this specific example. The level of skill in the art is high and it would not be a simple matter to create a toxin which can still act as a toxin in a limited fashion – by affecting one group of cells without affecting another, as evidenced by the prior art. In fact, as seen on the top left column of page 2424, the use of the toxin-chemokine conjugate was not as effective as the chemokine, alone, in down-regulating CCR5, adding to the further complexity of effective treatment using the claimed methods. Regarding the use of antibodies to decrease CCR5 in synovial fluid; this, again, was performed in vitro (ex vivo). Shah do not teach administering these antibodies to a patient in order to decrease CCR5

levels. Therefore, in contrast to Applicant's argument, the Examiner does have a basis for concluding that conjugates with other chemokines will target their receptors in a manner encompassed by the invention.

Applicants further argue that the claims, as amended, are not drawn to treating particular diseases. However, the claims do encompass (in fact, recite) "inhibiting the activation, proliferation or migration of immune cells that are involved in the inflammatory response" and Applicant states that he should be entitled to such a "generic invention." Applicant further argues that "the specification provides numerous chemokine targeting agents, identifies the association of expression of particular chemokine receptors in particular disease states or conditions and teaches how to select a chemokine targeting agent for a particular condition." Applicant has provided a cytotoxic assay which can demonstrate the effect of a compound on cell viability as well as a chemotactic assay (Example 2) and has tested OPL98110 in these assays. Though it was shown that this conjugate decreased cell viability in vitro, it has not been shown that these same effects would be expected in vivo. There is no evidence that the model used in the specification is an art-accepted model of cell toxicity in vivo. In addition, there appears to be no guidance or working examples that the designed conjugate, OPL98110, can inhibit cell migration, as claimed. Example 2 only demonstrates that the immune cells were killed once they migrated to a desired location. Furthermore, the Example only shows that activated T-lymphocytes were affected by OPL98110. However, the claims encompass immune cells other than T-lymphocytes. In addition, the claims recite that the conjugate will inhibit the activation of these cells. However, the specification only demonstrates that the conjugates have an effect on cells *which are already activated*. No effect on the ability of cells which have yet to become activated is seen.

Applicants also argue that Tables 2 and 3 teach how to select a conjugate based on the disease. Applicants have continued to argue that they are not attempting to treat a disease, only the underlying mechanism. However, Table 2 clearly demonstrates that the intention of the invention is to treat a disease and it appears from the Table that all one has to do is to simply chose whatever disease is to be treated and to administer the appropriate conjugate. Therefore, the intended use of the invention does appear to be the treatment of diseases. Again, though Applicant continually tries to distance himself from claiming the treatment of diseases using the claimed invention, statements such as that found on page 18 of the Response, which states "suppression of migration and activation of leukocytes can effectively treat such diseases" make the line between what is claimed and what is intended by the claims to be fine.

Even, arguendo, Applicants are not treating diseases, the subsequent filings as discussed on pages 21-22 of the Response discuss, in total, a small number of situations in which targeting immune cells may be used. Similarly, the examples in Tables 2 and 3 of the Response, in which the Examiner is only

focusing on the relevant "ligand-toxin fusion proteins," are, clearly, specific ligand-toxin fusion proteins which have a specific indication. The scope of Applicants' claims is much more excessive than these subsequent data. In fact, the drugs discussed in Table 2 for the most part are only used to the potential treatment of cancers. The scope of Applicants' invention is, again, much greater.

Applicant continues on page 17 of the Response by stating that "those of skill in the art know that conjugates will target their respective receptors, that the immune system can be targeted and modulation of immune system cells has therapeutic effect on a wide variety of diseases and conditions. This application provides a new way of modulating the immune system." This argument has been considered, but is not deemed persuasive. The bar for enablement, respectfully, is "make and use" not "make and test." Though Applicant has provided information as to the association of certain chemokines with certain diseases, the claims, when read in light of the specification, intend to treat diseases by having the artisan decide which conjugates to use at which time in the treatment process for the disease of interest. The question is not if the specification has taught how to make the conjugates, as the art demonstrates that physically making the conjugates is routine.

Regarding Brenner v. Manson, the Examiner was not questioning the utility of the present invention under 35 USC 101. The current situation is not analogous to Brenner v. Manson regarding utility. The Examiner was simply taking a quote from the decision to drive the point home that (1) benefit does not currently exist in the present form (2) the field is, in fact, broad and (3) a patent is not a hunting license. These points can correctly be made under an issue of enablement aside from utility. As stands, Applicants' invention is not enabled for the full breadth of the claims as discussed throughout this rejection, wherein certain pertinent phrases were only being summarized in the Examiner's statement of Brenner.

*Given the immense role of effector cells in basically everything from maintaining homeostasis to their involvement in potentially hundreds of diseases covering a broad spectrum of etiologies, it is undue experimentation for the artisan to determine the underlying cause of a particular disease with regard to the effector cell, sufficiently comprehend at which exact stage the disease is in at a given time, to identify which chemokine receptors are overexpressed, or are best targeted, while not targeting undesired cells, to monitor any changes in the leukocytes with regard to changes in chemokine receptor expression and possible function (since the claimed methods are, in fact, dealing with disease states, which could affect whole cells or individual receptors, including chemokine receptors and their pathways) in order to affect any potential immune effector cell in any potential activation state in order to inhibit activation,*

*proliferation or migration of these immune effector cell by altering metabolism or gene expression in the cell, regulating or altering protein synthesis in the cell, or killing the cell.*

It is believed that all pertinent arguments have been addressed.

***3. Conclusion***

A. No claim is allowable.

This is a CONTINUATION of applicant's earlier Application No. 09/360,242. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Advisory information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571) 272-0888. The examiner can normally be reached on M-Th 10 AM – 7 PM (eastern); alt F 10 AM – 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert Landsman

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PRIMARY EXAMINER